Access DB# 162089

163716

SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: Rebecca Look Examiner #: 69826 Date: 8/10/05

Art Unit: 1614 Phone Number 30 Serial Number: 10/685628

Mail Box and Bldg/Room Location: 3C70 Results Format Preferred (circle): PAPER DISK E-MAIL

If more than one search is submitted, please prioritize searches in order of need.

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Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of invention: _____

Inventors (please provide full names): See attached

_____

Earliest Priority Filing Date: _____

**For Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.*

Please provide structure of hydroxylansoprazole
& search it to treat gastroesophageal reflux disease

Thanks
Rebecca

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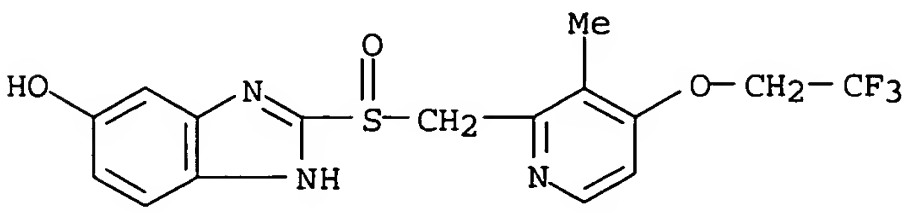
STAFF USE ONLY	Type of Search	Vendors and cost where applicable
Searcher: _____	NA Sequence (#)_____	STN _____
Searcher Phone #: _____	AA Sequence (#)_____	Dialog _____
Searcher Location: _____	Structure (#) _____	Questel/Orbit _____
Date Searcher Picked Up: _____	Bibliographic _____	Dr.Link _____
Date Completed: _____	Litigation _____	Lexis/Nexis _____
Searcher Prep & Review Time: _____	Fulltext _____	Sequence Systems _____
Clerical Prep Time: _____	Patent Family _____	WWW/Internet _____
Online Time _____	Other _____	Other (specify)_____

FTO-1590 (8-01)

=> d

L10 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2005 ACS on STN
RN **131926-98-2** REGISTRY
ED Entered STN: 08 Feb 1991
CN 1H-Benzimidazol-5-ol, 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 5-Hydroxylansoprazole
CN AG 1908
CN M-VI
FS 3D CONCORD
DR 166404-12-2
MF C16 H14 F3 N3 O3 S
SR CA
LC STN Files: ANABSTR, BIOSIS, CA, CAPLUS, CHEMCATS, TOXCENTER, USPATFULL



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

27 REFERENCES IN FILE CA (1907 TO DATE)
27 REFERENCES IN FILE CAPLUS (1907 TO DATE)
ED Entered STN: 08 Feb 1991

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=> d que stat l13
L10             1 SEA FILE=REGISTRY ABB=ON  131926-98-2/RN
L11            33 SEA FILE=HCAPLUS ABB=ON  L10 OR ?HYDROXYLANSOPRAZOLE?
L12            10 SEA FILE=HCAPLUS ABB=ON  L11 AND (?ULCER? OR ?GASTR? OR
                  ?ESOPHAG?)
L13             9 SEA FILE=HCAPLUS ABB=ON  L12 AND (PRD<20031014 OR PD<20031014)

=> d ibib abs l13 1-9

L13  ANSWER 1 OF 9  HCAPLUS  COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:         2003:652131  HCAPLUS
DOCUMENT NUMBER:          139:214237
TITLE:                    Preparation of nitrate prodrugs able to release nitric
                          oxide in a controlled and selective way and their use
                          for prevention and treatment of inflammatory, ischemic
                          and proliferative diseases
INVENTOR(S):              Scaramuzzino, Giovanni
PATENT ASSIGNEE(S):       Italy
SOURCE:                   Eur. Pat. Appl., 313 pp.
                          CODEN: EPXXDW
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.           KIND   DATE        APPLICATION NO.         DATE
     ---------------      ----   --------    --------------------    --------
     EP 1336602            A1    20030820    EP 2002-425075          20020213 <--
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, SI, LT, LV, FI, RO, MK, CY, AL, TR
PRIORITY APPLN. INFO.:                       EP 2002-425075          20020213 <--
GI
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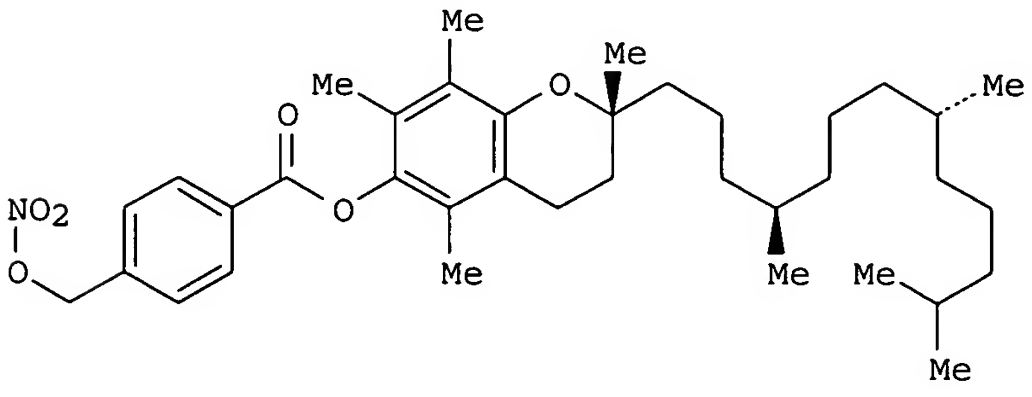


II

AB New pharmaceutical compds. of general formula F-(X)q (I) [q = 1-5, preferably 1; F is chosen among drugs such as δ-tocopherol, clidanac, diethylhomospermine, glucosamine, thymocartin, vofopitant, etc.; X is chosen among 4 groups M, T, V, and Y where M = ONO2, nitrate salt, nitrite ester, ONO, thoinitrite, SNO, etc., T = OR1-M, OR1OR1-M, SR1NR2R1-M, NR2R1-M, NR2R1SR1-M, etc., R1 = saturated or unsatd., linear or branched alkylene, having 1 to 21 carbon atoms or a saturated or unsatd., optionally heterosubstituted or branched cycloalkylene, having 3 to 7 carbon atoms or an optionally heterosubstituted arylene having 3 to 7 carbon atoms; R2 = H, saturated or unsatd., linear or branched 1-21 carbon atom alkyl, saturated or unsatd. optionally heterosubstituted or branched 3-7 carbon cycloalkyl, optionally heterosubstituted 3-7 carbon aryl; R1, R2 =

OH, SH, F, Cl, Br, OPO3H2, CO2H, etc.; bond between F and T = carboxylic ester, carboxylic amide, glycoside, azo, thioester, sulfonic ester, etc.; V = Z-M2, OZ-M2, NR2Z-M2, R1Z-M2, OR1-M2, OR1Z-M2, M2 = M, R1-M, OR1-M, SR1-M, NR2R1-M; ZM2 = COCH2CH(M2)CH2N+Me3, COCH2CH2COM2, COCH(NHR2)CH2M2, etc.; Y = 4-COC6H4CH2ONO2, O(CH2)4ONO2, COCH(NH2)CH2ONO2, 3-OC6H4CH2ONO2, etc.] were prepared For example, α-tocopherol reacted with 4-HO2CC6H4CH2ONO2 to give the nitroxymethyl derivative II. The compds. of general formula I are nitrate prodrugs which can release nitric oxide in vivo in a controlled and selective way and without hypotensive side effects and for this reason they are useful for the preparation of medicines for prevention and treatment of inflammatory, ischemic, degenerative and proliferative diseases of musculoskeletal, tegumental, respiratory, **gastrointestinal**, genito-urinary and central nervous systems.

REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 2 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:226298 HCAPLUS
DOCUMENT NUMBER: 139:79086
TITLE: A Novel Antioxidant and Antiapoptotic Role of Omeprazole to Block **Gastric Ulcer** through Scavenging of Hydroxyl Radical
AUTHOR(S): Biswas, Kaushik; Bandyopadhyay, Uday; Chattopadhyay, Ishita; Varadaraj, Archana; Ali, Esahak; Banerjee, Ranajit K.
CORPORATE SOURCE: Department of Physiology, Indian Institute of Chemical Biology, Kolkata, 700 032, India
SOURCE: Journal of Biological Chemistry (**2003**), 278(13), 10993-11001
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The mechanism of the **antiulcer** effect of omeprazole was studied placing emphasis on its role to block oxidative damage and apoptosis during **ulceration.** Dose-response studies on **gastroprotection** in stress and indomethacin-induced **ulcer** and inhibition of pylorus ligation-induced acid secretion indicate that omeprazole significantly blocks **gastric** lesions at lower dose (2.5 mg/kg) without inhibiting acid secretion, suggesting an independent mechanism for its **antiulcer** effect. Time course studies on **gastroprotection** and acid reduction also indicate that omeprazole almost completely blocks lesions at 1 h when acid inhibition is partial. The severity of lesions correlates well with the increased level of endogenous hydroxyl radical (·OH), which when scavenged by DMSO causes around 90% reduction of the lesions, indicating that ·OH plays a major role in **gastric** damage. Omeprazole blocks stress-induced increased generation of ·OH and associated lipid peroxidn. and protein oxidation, indicating that its antioxidant role plays a major part in preventing oxidative damage. Omeprazole also prevents stress-induced DNA fragmentation, suggesting its antiapoptotic role to block cell death during **ulceration.** The oxidative damage of DNA by ·OH generated in vitro is also protected by omeprazole or its analog, lansoprazole. Lansoprazole when incubated in a ·OH-generating system scavenges ·OH to produce four oxidation products of which the major one in mass spectroscopy shows a mol. ion peak at m/z 385, which is 16 mass units higher than that of lansoprazole (m/z 369). The product shows no addnl. aromatic proton signal for aromatic hydroxylation in 1H NMR.

The product absorbing at 278 nm shows no alkaline shift for phenols, thereby excluding the formation of **hydroxylansoprazole.** The product is assigned to lansoprazole sulfone formed by the addition of one oxygen atom at the sulfur center following attack by the ·OH. Thus, omeprazole plays a significant role in **gastroprotection** by acting as a potent antioxidant and antiapoptotic mol.

REFERENCE COUNT: 84 THERE ARE 84 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 3 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:662644 HCAPLUS
DOCUMENT NUMBER: 138:214821
TITLE: Enantioselective disposition of lansoprazole in extensive and poor metabolizers of CYP2C19
AUTHOR(S): Kim, Kyoung-Ah; Shon, Ji-Hong; Park, Ji-Young; Yoon, Young-Ran; Kim, Min-Jung; Yun, Doo-Hee; Kim, Moon-Kyung; Cha, In-June; Hyun, Myung-Ho; Shin, Jae-Gook
CORPORATE SOURCE: Department of Pharmacology, Inje University College of Medicine and Clinical Pharmacology Center, Pusan Paik Hospital, Pusan National University, Pusan, S. Korea
SOURCE: Clinical Pharmacology & Therapeutics (St. Louis, MO, United States) (**2002**), 72(1), 90-99
CODEN: CLPTAT; ISSN: 0009-9236
PUBLISHER: Mosby, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The objective was to evaluate the enantioselective disposition of lansoprazole in relation to the genetic polymorphism of CYP2C19. Methods: A single oral dose of racemic lansoprazole (30 mg) was administered to 6 extensive metabolizers and 6 poor metabolizers whose genotypes were determined by use of polymerase chain reaction-restriction fragment length polymorphism. The pharmacokinetic parameters were estimated from the blood plasma concns. of lansoprazole racemate, its enantiomers, and metabolites, which were measured for 24 h after drug administration. The unbound fraction of lansoprazole enantiomers was determined by ultra-filtration of fresh human serum spiked with racemic lansoprazole. Results: The plasma concns. of R(+)-lansoprazole were consistently higher than those of the S(-)enantiomer in both extensive and poor metabolizers of CYP2C19, and the mean area under the plasma concentration-time curve of the (+)- and (-)-enantiomers showed 4.3- and 5.8-fold differences between poor and extensive metabolizers, resp. The (+)/(-) ratios of lansoprazole clearance were not significantly different between poor and extensive metabolizers (0.19 and 0.05, resp.). The values for volume of distribution of the (-)-enantiomer were 3- and 10-fold greater, resp., than those of the (+)-enantiomer in poor and extensive metabolizers, which was related to a 2-fold higher unbound fraction of the (-)-enantiomer. Conclusions: The effect of CYP2C19 genetic polymorphism on the enantioselective disposition of lansoprazole seems to be less significant than the effect on omeprazole and pantoprazole. The disposition of lansoprazole enantiomers appears to be influenced by enantioselective protein binding and by enantioselective metabolism of lansoprazole.

REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 4 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:662635 HCAPLUS
DOCUMENT NUMBER: 137:226453
TITLE: Dose-dependent inhibition of CYP3A activity by

clarithromycin during Helicobacter pylori eradication therapy assessed by changes in plasma lansoprazole levels and partial cortisol clearance to 6β-hydroxycortisol

AUTHOR(S): Ushiama, Hideki; Echizen, Hirotoshi; Nachi, Shinobu; Ohnishi, Akihiro

CORPORATE SOURCE: Department of Laboratory Medicine, Daisan Hospital, Jikei University School of Medicine, Tokyo, Japan

SOURCE: Clinical Pharmacology & Therapeutics (St. Louis, MO, United States) (2002), 72(1), 33-43
CODEN: CLPTAT; ISSN: 0009-9236

PUBLISHER: Mosby, Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Objective: A 7-day triple therapy with lansoprazole, amoxicillin (INN, amoxicillin), and clarithromycin is widely used for eradication of Helicobacter pylori. Because clarithromycin is a potent inhibitor of cytochrome P 450 (CYP) 3A, we investigated whether the standard triple therapy with clarithromycin would elicit clin. relevant CYP3A inhibition and alter CYP3A-mediated lansoprazole disposition in H pylori-pos. patients. Methods: Twenty H pylori-pos. patients with peptic **ulcer** disease were randomly assigned to 2 groups: One group received 200 mg clarithromycin, 30 mg lansoprazole, and 750 mg amoxicillin at 8 am and 8 pm for 7 days; the other group received 400 mg clarithromycin, 30 mg lansoprazole, and 750 mg amoxicillin at 8 am and 8 pm for 7 days. Ten healthy control subjects received 30 mg lansoprazole and 750 mg amoxicillin at 8 am and 8 pin for 7 days but did not receive clarithromycin. Urine samples were collected for 3 h (from 8 am to 11 am) for urinary 6β-hydroxycortisol and cortisol assay, and midpoint (at 9:30 am) plasma samples for cortisol assay were obtained from all participants before the drug therapy (day 0) and on day 7. In vivo CYP3A activity was assessed by the partial cortisol clearance by means of the formation of 6β-hydroxycortisol (CLcortisol→6β-hydroxycortisol) and the urinary 6β-hydroxycortisol/cortisol ratio. Addnl. plasma samples for lansoprazole, 5-**hydroxylansoprazole**, and lansoprazole sulfone assay were obtained at 11 am on day 7. Results: The groups of patients given 400 and 800 mg/day clarithromycin for H pylori eradication therapy showed 39% (from 2.20 ± 1.29 to 1.35 ± 0.88 mL/min [day 0 vs. 7, mean ± SD]; $P < .05$) and 68% (2.40 ± 1.22 to 0.76 ± 0.51 mL/min; $P < .05$) redns. in CLcortisol→6β-hydroxycortisol, resp. In contrast, the control subjects given lansoprazole and amoxicillin without clarithromycin showed no significant changes in CLcortisol→6β-hydroxycortisol. The urinary 6β-hydroxycortisol/cortisol ratio also decreased significantly ($P < .05$) in the patient groups but not in the control subjects. The mean 3-h plasma lansoprazole levels elevated in proportion to the doses of clarithromycin: 385 ± 338 ng/mL for the control subjects, 696 ± 797 ng/mL for the H pylori-pos. patients given 400 mg/day clarithromycin, and 947 ± 806 ng/mL for the H pylori-pos. patients given 800 mg/day clarithromycin ($P < .05$ vs. the control subjects). No significant differences were observed among the groups in the mean plasma ratios of 5-**hydroxylansoprazole** or lansoprazole sulfone to lansoprazole. Conclusions: The 7-day H pylori eradication therapy with clarithromycin, amoxicillin, and lansoprazole may elicit substantial inhibition of in vivo CYP3A activity. Although resultant elevations in plasma lansoprazole concns. may be beneficial for H pylori eradication, caution must be exercised for possible drug interaction with a concomitantly administered CYP3A substrate (s) in patients undergoing H pylori eradication therapy with clarithromycin, amoxicillin, and lansoprazole.

REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 5 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:17375 HCAPLUS
DOCUMENT NUMBER: 136:226583
TITLE: Effect of high-dose lansoprazole on intragastic pH in subjects who are homozygous extensive metabolizers of cytochrome P4502C19
AUTHOR(S): Furuta, Takahisa; Shirai, Naohito; Xiao, Fang; Ohashi, Kyoichi; Ishizaki, Takashi
CORPORATE SOURCE: First Department of Medicine and Department of Clinical Pharmacology, Hamamatsu University School of Medicine, Hamamatsu, Japan
SOURCE: Clinical Pharmacology & Therapeutics (St. Louis, MO, United States) (**2001**), 70(5), 484-492
CODEN: CLPTAT; ISSN: 0009-9236
PUBLISHER: Mosby, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Lansoprazole is mainly metabolized by cytochrome P 4502C19 (CYP2C19) in the liver. The effect of lansoprazole is assumed to be insufficient in subjects who are homozygous extensive metabolizers of CYP2C19. This study aimed to examine whether the CYP2C19 genotype status affected the acid-inhibitory effects of lansoprazole and to develop a strategy to overcome this pharmacogenetic problem. Eighteen Helicobacter pylori-neg. healthy volunteers, whose CYP2C19 genotypic status had been assessed, participated in the study. They consisted of 7 subjects who were homozygous extensive metabolizers, 7 subjects who were heterozygous extensive metabolizers, and 4 subjects who were poor metabolizers of CYP2C19, who took a placebo or lansoprazole 30 mg once daily in the morning for 8 days. On day 8 of dosing, 24-h **intragastric** pH values were recorded. Five of the homozygous extensive metabolizer subjects underwent the 24-h **intragastric** pH monitoring on day 8 of dosing of lansoprazole 30 mg 4 times daily. When lansoprazole 30 mg was given once daily, the mean 24-h **intragastric** pH values in the subjects who were homozygous extensive metabolizers, heterozygous extensive metabolizers, and poor metabolizers were 4.5, 4.9, and 5.5, resp. ($P < .005$). On day 8 of dosing of lansoprazole 30 mg 4 times daily in subjects who were homozygous extensive metabolizers, the mean 24-h **intragastric** pH value was 7.4. The effect of lansoprazole on **intragastric** pH depended significantly on CYP2C19 genotype status. Complete acid inhibition could be achieved by the frequent administration of lansoprazole (eg, 30 mg 4 times daily) in subjects who were homozygous extensive metabolizers. A genotyping test of CYP2C19 status appears useful for prescribing an optimal dosing scheme of lansoprazole.

REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 6 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:84622 HCAPLUS
DOCUMENT NUMBER: 132:141954
TITLE: Pharmaceutical compositions comprising **hydroxylansoprazole** for **ulcer** treatment
INVENTOR(S): Yelle, William E.
PATENT ASSIGNEE(S): Sepracor Inc., USA
SOURCE: PCT Int. Appl., 18 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2000004904	A1	20000203	WO 1999-US16322		19990719 <--
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM					
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG					
CA 2337886	AA	20000203	CA 1999-2337886		19990719 <--
AU 9952182	A1	20000214	AU 1999-52182		19990719 <--
AU 763642	B2	20030731			
EP 1098648	A1	20010516	EP 1999-937321		19990719 <--
EP 1098648	B1	20021002			
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO					
JP 2002521336	T2	20020716	JP 2000-560897		19990719 <--
AT 225175	E	20021015	AT 1999-937321		19990719 <--
ES 2182554	T3	20030301	ES 1999-937321		19990719 <--
US 6335351	B1	20020101	US 1999-357458		19990720 <--
US 2002099079	A1	20020725	US 2001-46464		20011019 <--
US 2004077688	A1	20040422	US 2003-685628		20031014 <--
PRIORITY APPLN. INFO.:			US 1998-93762P	P	19980722 <--
			WO 1999-US16322	W	19990719 <--
			US 1999-357458	A3	19990720 <--
			US 2001-46464	B1	20011019 <--

AB A pharmaceutical composition for treating humans suffering from **ulcers** of stomach, duodenum, and **esophagus, gastroesophageal** reflux diseases, Zollinger-Ellison Syndrome, and other disorders associated with **gastric** hyperactivity comprises 5-**hydroxylansoprazole** or a pharmaceutically acceptable salt thereof. **Hydroxylansoprazole** exhibits a lessened liability toward drug-drug interactions and a more predictable dosing regimen than its parent compound, lansoprazole. **Hydroxylansoprazole** inhibits the H+,K+-ATPase associated with the **gastric** proton pump and the resulting secretion of **gastric** acid by parietal cells. The invention also relates to a method of treating psoriasis using **hydroxylansoprazole.** A dry granulate, prepared from dry mixture containing **hydroxylansoprazole** 250 mg, colloidal silica 8 mg, and Mg stearate 1 mg, was mixed with croscarmellose 60 mg, crystalline cellulose 190 mg, and talc 10 mg and compressed into tablets.

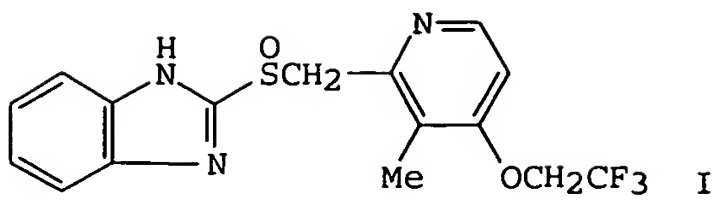
REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 7 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:686268 HCAPLUS
DOCUMENT NUMBER: 123:132521
TITLE: Mechanism for species-specific induction of Leydig cell tumors in rats by lansoprazole
AUTHOR(S): Fort, F. L.; Miyajima, H.; Ando, T.; Suzuki, T.; Yamamoto, M.; Hamashima, T.; Sato, S.; Kitazaki, T.;

Mahony, M. C.; et al.
CORPORATE SOURCE: Abbott Laboratories, Abbott Park, IL, 60064, USA
SOURCE: Fundamental and Applied Toxicology (**1995**), 26(2), 191-202
CODEN: FAATDF; ISSN: 0272-0590
PUBLISHER: Academic
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Lansoprazole is a substituted benzimidazole which inhibits **gastric** acid secretion by inhibiting the hydrogen-potassium ATPase (proton pump) in the parietal cell. The finding of Leydig cell hyperplasia and Leydig cell tumors in 2-yr oral studies in Sprague-Dawley rats but not in CD-1 mice promoted investigative studies to determine the mechanism for the Leydig cell changes. HCG challenge studies in Sprague-Dawley rats revealed decreased testosterone responsiveness in rats treated orally for 1 or 2 wk with lansoprazole. After 4 wk of daily oral treatment increases in serum LH and decreases in serum testosterone were detected within a few hours after dosing. In a study where 9-mo-old male F344 rats were given testosterone supplementation via Silastic implants and then treated with lansoprazole for 6 mo, a high incidence of Leydig cell tumors was seen in lansoprazole-treated, unsupplemented rats, whereas no Leydig cell tumors were seen in testosterone supplemented rats. This implied that reduction of the normal feedback inhibition at the level of the hypothalamus and/or pituitary due to reduced testosterone levels, thus giving rise to elevated levels of LH, was involved in the induction of Leydig cell tumors by lansoprazole. In vitro studies with Leydig cells from rats using various stimulators and precursors of testosterone biosynthesis demonstrated that the most sensitive site for inhibition of testosterone synthesis by lansoprazole is the transport of cholesterol to the cholesterol side chain cleavage enzyme. The IC50s for inhibition of LH or hCG-stimulated testosterone synthesis in Leydig cells from rats, mice, and monkeys were 11-12, 8, and 27.4 μg/mL, resp. In vitro studies with metabolites of lansoprazole revealed that three metabolites were more potent inhibitors of testosterone synthesis than the parent drug, two of them being at least 10 times more potent. These metabolites are present in rats at substantial levels but are undetectable in humans. The lack of induction of Leydig cells tumors in mice, lower sensitivity of primate Leydig cells, and the absence of testosterone synthesis-inhibiting metabolites in man suggest that Leydig cell tumors found in rats represent a species-specific sensitivity and does not imply a risk for clin. use in man.

L13 ANSWER 8 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1991:421996 HCAPLUS
DOCUMENT NUMBER: 115:21996
TITLE: Effects of AG-1749 (lansoprazole) and its metabolites on acid secretion and experimental **ulcers**
AUTHOR(S): Inatomi, Nobuhiro; Nagaya, Hideaki; Ishisaka, Yoichi; Satoh, Hiroshi
CORPORATE SOURCE: Res. Dev. Div., Takeda Chem. Ind., Ltd., Japan
SOURCE: Yakuri to Chiryo (1973-2000) (**1991**), 19(2), 477-86
CODEN: YACHDS; ISSN: 0386-3603
DOCUMENT TYPE: Journal
LANGUAGE: Japanese
GI



I

AB The effects of AG-1749 (I) and its metabolites on canine microsomal (H++K+)-ATPase, acid formation in canine **gastric** parietal cells, **gastric** acid secretion in rats and dogs, and exptl. stomach and duodenal **ulcers** in rats were studied. AG-1749 inhibited (H++K+)-ATPase activity in canine microsomes and acid formation in canine parietal cells stimulated by dibutyryl cAMP in a concentration -dependent manner.

The IC50 values were 6.3 and 0.09 μM, resp. The hydroxy metabolite inhibited (H++K+)-ATPase activity with IC50 = 3 μM, but it did not inhibit acid formation in isolated parietal cells. The sulfonyl metabolite affected neither microsomal (H++K+)-ATPase activity nor acid formation in parietal cells. AG-1749 inhibited histamine-stimulated acid secretion in dogs and rats; the ID50 values were 0.14 mg/kg i.v. and 0.4 mg/kg i.p., resp. Neither metabolite inhibited acid secretion in dogs and rats at 1 mg/kg i.v. and 10 mg/kg i.p. AG-1749 inhibited reflux **esophagitis**, water-immersion stress-induced **gastric** lesions, and mepirizole-induced duodenal **ulcers** in rats in a dose-dependent manner; ID50 values were 0.4, 0.7, and <0.1 mg/kg, i.p., resp. The metabolites barely inhibited the exptl. **ulcers.** The antisecretory and **antiulcer** effects by AG-1749 are exerted mainly by AG-1749 itself and not by its 2 metabolites.

L13 ANSWER 9 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1991:74645 HCAPLUS
DOCUMENT NUMBER: 114:74645
TITLE: Metabolic fate of AG-1749, a new proton pump inhibitor, in rats, mice, and dogs
AUTHOR(S): Miwa, Kiyoshi; Mitani, Masayoshi; Tsukamoto, Takeshi; Yoshida, Kiyoshi; Kobayashi, Takuo; Kimura, Tomokazu; Shimomura, Hatsushi; Tanayama, Shigeharu
CORPORATE SOURCE: Drug-Saf. Res. Lab., Takeda Chem. Ind., Ltd., Japan
SOURCE: Yakuri to Chiryo (1973-2000) (**1990**), 18(9), 3413-35
CODEN: YACHDS; ISSN: 0386-3603
DOCUMENT TYPE: Journal
LANGUAGE: Japanese

AB The absorption, tissue distribution, metabolism, and elimination of [14C]AG-1749 following oral administration were studied in rats, mice, and dogs. The results show that the absorption rate in rats, mice and dogs was 37, 28, and 63%, resp., and that the bioavailability was 4, 4, and 23%, resp. AG-1749 distributed preferentially in **gastrointestinal** tract and liver. Ten major metabolites of AG-1749 were determined in blood plasma, bile, and urine. The unchanged compound and metabolites were able to transfer to fetus and milk. The metabolites were mainly excreted in feces, suggesting the role of enterohepatic circulation. In addition, AG-1749 induced drug-metabolizing enzymes in liver after oral administration.

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=> d que stat l15
L10             1 SEA FILE=REGISTRY ABB=ON  131926-98-2/RN
L11            33 SEA FILE=HCAPLUS ABB=ON  L10 OR ?HYDROXYLANSOPRAZOLE?
L12            10 SEA FILE=HCAPLUS ABB=ON  L11 AND (?ULCER? OR ?GASTR? OR
                  ?ESOPHAG?)
L14            26 SEA L12
L15            17 DUP REMOV L14 (9 DUPLICATES REMOVED)

=> d ibib abs l15 1-17

L15  ANSWER 1 OF 17  BIOSIS  COPYRIGHT (c) 2005 The Thomson Corporation  on STN
ACCESSION NUMBER:    2005:175661  BIOSIS
DOCUMENT NUMBER:     PREV200500173832
TITLE:               Determination of lansoprazole and two of its metabolites by
                     liquid-liquid extraction and automated column- switching
                     high-performance liquid chromatography: application to
                     measuring CYP2C19 activity.
AUTHOR(S):           Uno, Tsukasa; Yasui-Furukori, Norio [Reprint Author];
                     Takahata, Takenori; Sugawara, Kazunobu; Tateishi, Tomonori
CORPORATE SOURCE:    Sch MedDept Clin Pharmacol, Hirosaki Univ, 5 Zaifu,
                     Hirosaki, Aomori, 0368562, Japan
                     yasufuru@cc.hirosaki-u.ac.jp
SOURCE:              Journal of Chromatography B, (February 25 2005) Vol. 816,
                     No. 1-2, pp. 309-314. print.
                     ISSN: 1570-0232 (ISSN print).
DOCUMENT TYPE:       Article
LANGUAGE:            English
ENTRY DATE:          Entered STN: 4 May 2005
                     Last Updated on STN: 4 May 2005
AB   A simple and sensitive column-switching high-performance liquid
     chromatographic (HPLC) method for the simultaneous determination of
     lansoprazole, a proton pump inhibitor and its major metabolites: 5-
     hydroxylansoprazole and lansoprazole sulfone in human plasma.  The
     test compounds were extracted from 1 mL of plasma using diethyl
     ether-dichloromethane (7:3, v/v) mixture and the extract was injected into
     a column I (TSK-PW precolumn, 10 mum, 3.5 mm x 4.6 mm W.) for clean-up and
     column I (C18 STR ODS-II analytical column, 5 mum, 150 mm x 4.6 mm i.d.)
     for separation.  The peak was detected by a ultraviolet detector set at a
     wavelength of 285 nm, and the total time for a chromatographic separation
     was apprx25 min.  The method was validated for the concentration range
     from 3 to 5000 ng/mL.  Mean recoveries were 74.0 % for lansoprazole, 68.3
     % for 5-hydroxylansoprazole, and 79.4 % for lansoprazole
     sulfone.  Intra- and inter-day relative standard derivatives were less
     than 6.1 and 5.1 % for lansoprazole, 5.8 and 5.8 % for 5-
     hydroxylansoprazole, 4.4 and 5.9 % for lansoprazole sulfone,
     respectively, at the different concentration ranges.  This method is
     suitable for use in therapeutic drug monitoring and pharmacokinetic
     studies, and provides use tool for measuring CYP2C19 activity.  Copyright
     2004 Elsevier B.V.  All rights reserved.

L15  ANSWER 2 OF 17     MEDLINE on STN                    DUPLICATE 1
ACCESSION NUMBER:    2004525739     MEDLINE
DOCUMENT NUMBER:     PubMed ID: 15496639
TITLE:               Effects of fluvoxamine on lansoprazole pharmacokinetics in
                     relation to CYP2C19 genotypes.
AUTHOR:              Yasui-Furukori Norio; Saito Masato; Uno Tsukasa; Takahata
                     Takenori; Sugawara Kazunobu; Tateishi Tomonori
CORPORATE SOURCE:    Department of Clinical Pharmacology, Hirosaki University,
                     School of Medicine, Hirosaki 036-8562, Japan.
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SOURCE: Journal of clinical pharmacology, (2004 Nov) 44 (11) 1223-9.
Journal code: 0366372. ISSN: 0091-2700.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200502
ENTRY DATE: Entered STN: 20041022
Last Updated on STN: 20050205
Entered Medline: 20050204

AB Lansoprazole is a substrate of CYP2C19 and CYP3A4. The aim of this study was to compare the inhibitory effects of fluvoxamine, an inhibitor of CYP2C19, on the metabolism of lansoprazole between CYP2C19 genotypes. Eighteen volunteers--of whom 6 were homozygous extensive metabolizers (EMs), 6 were heterozygous EMs, and 6 were poor metabolizers (PMs) for CYP2C19--received three 6-day courses of either daily 50 mg fluvoxamine or placebo in a randomized fashion with a single oral 60-mg dose of lansoprazole on day 6 in all cases. Plasma concentrations of lansoprazole and its metabolites, 5-**hydroxylansoprazole** and lansoprazole sulfone, were monitored up to 24 hours after the dosing. During placebo administration, there was a significant difference in the area under the plasma concentration-time curve from time 0 to infinity (AUC(0-infinity)) of lansoprazole between CYP2C19 genotypes. Fluvoxamine treatment increased AUC(0-infinity) of lansoprazole by 3.8-fold ($P < .01$) in homozygous EMs and by 2.5-fold ($P < .05$) in heterozygous EMs, whereas no difference in any pharmacokinetic parameters was found in PMs. There was a significant difference in the fluvoxamine-mediated percentage increase in the AUC(0-infinity) of lansoprazole between CYP2C19 genotypes. The present study indicates that there are significant drug interactions between lansoprazole and fluvoxamine in EMs. CYP2C19 is predominantly involved in lansoprazole metabolism in EMs.

L15 ANSWER 3 OF 17 MEDLINE on STN

ACCESSION NUMBER: 2004593732 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15448955
TITLE: Pharmacokinetic differences between the enantiomers of lansoprazole and its metabolite, 5-**hydroxylansoprazole**, in relation to CYP2C19 genotypes.
AUTHOR: Miura M; Tada H; Yasui-Furukori N; Uno T; Sugawara K; Tateishi T; Suzuki T
CORPORATE SOURCE: Department of Pharmacy, Akita University Hospital, 1-1-1 Hondo, 010-8543, Akita, Japan.
SOURCE: European journal of clinical pharmacology, (2004 Nov) 60 (9) 623-8. Electronic Publication: 2004-09-23.
Journal code: 1256165. ISSN: 0031-6970.
PUB. COUNTRY: Germany: Germany, Federal Republic of
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200504
ENTRY DATE: Entered STN: 20041130
Last Updated on STN: 20050402
Entered Medline: 20050401

AB OBJECTIVE: The purpose of this study was to elucidate the pharmacokinetics

of each enantiomer of lansoprazole and 5-**hydroxylansoprazole** in three different CYP2C19 genotype groups of Japanese subjects. METHODS: Healthy subjects (n=18), of whom 6 were homozygous extensive metabolizers (homEMs), 6 were heterozygous extensive metabolizers (hetEMs) and 6 were poor metabolizers (PMs), participated in the study. After a single oral dose of 60 mg of racemic lansoprazole, the plasma concentrations of the lansoprazole enantiomers, 5-**hydroxylansoprazole** enantiomers and lansoprazole sulfone were measured for 24 h post-dose. RESULTS: The plasma concentrations of (R)-lansoprazole were remarkably higher in all three CYP2C19 genotype groups than those of the corresponding (S)-enantiomer. The mean maximum plasma concentration (C(max)) of (S)-lansoprazole differed significantly among the three groups, whereas there was no difference for the (R)-enantiomer. The relative area under the plasma concentration (AUC) ratios of (R)- and (S)-lansoprazole in the homEMs, hetEMs, and PMs were 1:1.5:4.0 and 1:1.8:7.4, respectively. Yet, the relative AUC ratios of 5-**hydroxylansoprazole** to lansoprazole for the (R)- and (S)-enantiomers in the homEMs, hetEMs, and PMs were almost the same (1:0.73:0.12 and 1:0.77:0.13, respectively). However, the AUC ratios of the (S)-enantiomer were 13-fold greater for the three CYP2C19 genotypes than those of the corresponding (R)-enantiomer. CONCLUSIONS: The magnitude of the contribution of CYP2C19 to the 5-hydroxylation of (S)-lansoprazole was greater than that of the (R)-enantiomer. The R/S ratios for the AUC of lansoprazole for the homEMs, hetEMs and PMs were 12.7, 8.5 and 5.8, respectively, suggesting a significant effect of CYP2C19 polymorphisms on the stereoselective disposition of lansoprazole.

L15 ANSWER 4 OF 17 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 2003137096 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12529378
TITLE: A novel antioxidant and antiapoptotic role of omeprazole to block **gastric ulcer** through scavenging of hydroxyl radical.
AUTHOR: Biswas Kaushik; Bandyopadhyay Uday; Chattopadhyay Ishita; Varadaraj Archana; Ali Esahak; Banerjee Ranajit K
CORPORATE SOURCE: Department of Physiology, Indian Institute of Chemical Biology, 4, Raja S. C. Mullick Road, Kolkata 700 032, India.
SOURCE: Journal of biological chemistry, (2003 Mar 28) 278 (13) 10993-1001. Electronic Publication: 2003-01-15. Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200305
ENTRY DATE: Entered STN: 20030325
Last Updated on STN: 20030503
Entered Medline: 20030502

AB The mechanism of the **antiulcer** effect of omeprazole was studied placing emphasis on its role to block oxidative damage and apoptosis during **ulceration.** Dose-response studies on **gastroprotection** in stress and indomethacin-induced **ulcer** and inhibition of pylorus ligation-induced acid secretion indicate that omeprazole significantly blocks **gastric** lesions at lower dose (2.5 mg/kg) without inhibiting acid secretion, suggesting an independent mechanism for its **antiulcer** effect. Time course studies on **gastroprotection** and acid reduction also indicate that omeprazole almost completely blocks lesions at 1 h when acid inhibition is partial.

The severity of lesions correlates well with the increased level of endogenous hydroxyl radical (*OH), which when scavenged by dimethyl sulfoxide causes around 90% reduction of the lesions, indicating that *OH plays a major role in **gastric** damage. Omeprazole blocks stress-induced increased generation of *OH and associated lipid peroxidation and protein oxidation, indicating that its antioxidant role plays a major part in preventing oxidative damage. Omeprazole also prevents stress-induced DNA fragmentation, suggesting its antiapoptotic role to block cell death during **ulceration.** The oxidative damage of DNA by *OH generated in vitro is also protected by omeprazole or its analogue, lansoprazole. Lansoprazole when incubated in a *OH-generating system scavenges *OH to produce four oxidation products of which the major one in mass spectroscopy shows a molecular ion peak at m/z 385, which is 16 mass units higher than that of lansoprazole (m/z 369). The product shows no additional aromatic proton signal for aromatic hydroxylation in (1)H NMR. The product absorbing at 278 nm shows no alkaline shift for phenols, thereby excluding the formation of **hydroxylansoprazole.** The product is assigned to lansoprazole sulfone formed by the addition of one oxygen atom at the sulfur center following attack by the *OH. Thus, omeprazole plays a significant role in **gastroprotection** by acting as a potent antioxidant and antiapoptotic molecule.

L15 ANSWER 5 OF 17 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 2002:144673 BIOSIS
DOCUMENT NUMBER: PREV200200144673
TITLE: **Hydroxylansoprazole** compositions and methods.
AUTHOR(S): Yelle, William E. [Inventor]
CORPORATE SOURCE: ASSIGNEE: Sepracor Inc.
PATENT INFORMATION: US 6335351 20020101
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (Jan. 1, 2002) Vol. 1254, No. 1. http://www.uspto.gov/web/menu/patdata.html. e-file. CODEN: OGUPE7. ISSN: 0098-1133.
DOCUMENT TYPE: Patent
LANGUAGE: English
ENTRY DATE: Entered STN: 14 Feb 2002
Last Updated on STN: 26 Feb 2002
AB Methods and compositions are disclosed utilizing **hydroxylansoprazole** for the treatment of **ulcers** in humans. **Hydroxylansoprazole** exhibits a lessened liability toward drug-drug interactions than lansoprazole and a more predictable dosing regimen than lansoprazole. **Hydroxylansoprazole** is also usefull for the treatment of **gastroesophageal** reflux and other conditions related to **gastric** hypersecretion such as Zollinger-Ellison Syndrome.

L15 ANSWER 6 OF 17 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2002174381 EMBASE
TITLE: Comparison of the kinetic disposition of and serum **gastrin** change by lansoprazole versus rabeprazole during an 8-day dosing scheme in relation to CYP2C19 polymorphism.
AUTHOR: Ieiri I.; Kishimoto Y.; Okochi H.; Momiyama K.; Morita T.; Kitano M.; Morisawa T.; Fukushima Y.; Nakagawa K.; Hasegawa J.; Otsubo K.; Ishizaki T.
CORPORATE SOURCE: I. Ieiri, Department of Hospital Pharmacy, Faculty of Medicine, Tottori University, Nishi-machi 36-1, Yonago

683-8504, Japan. ieiri-ttr@umin.ac.jp
SOURCE: Cancer Chemotherapy and Pharmacology, Supplement, (2002) Vol. 49, No. 7, pp. 485-492.
Refs: 43
ISSN: 0943-9404 CODEN: CCHSET
COUNTRY: Germany
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 022 Human Genetics
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20020530
Last Updated on STN: 20020530
AB Background: Little is known about differences in the disposition kinetics and pharmacological effects on **gastrin** levels between lansoprazole and rabeprazole given in a repeated dosing scheme with respect to the polymorphic CYP2C19. Aim: To provide preliminary information that should be considered when prescribing proton-pump inhibitors (PPIs) for the treatment of acid-related diseases with reference to the CYP2C19 genotypic status. Methods: Helicobacter pylori-negative healthy volunteers were divided into the following three groups (n=5 each) on the basis of genotyping for CYP2C19: homozygous (hmEMs) and heterozygous extensive metabolizers (htEMs), and poor metabolizers (PMs). All received once-daily 30-mg doses of lansoprazole or 10-mg doses of rabeprazole during an 8-day course in a crossover manner. Results: The relative values for the area under the serum concentration-time curve (AUC) of lansoprazole and rabeprazole in the hmEMs, htEMs, and PMs after the final doses were 1:1.7:3.9 and 1:1.7:3.8, respectively. The relative AUCs of **gastrin** in the hmEMs, htEMs, and PMs were 1.6:2.6:3.1 for lansoprazole and 1.6:2.6:2.9 for rabeprazole, respectively. Conclusion: The disposition kinetic behavior of the two PPIs is co-segregated with CYP2C19. The magnitude of CYP2C19-dependent drug availability in the systemic circulation and resulting **gastrin** response appears to be fairly similar between the two drugs within the same CYP2C19 genotypic groups after a multiple-dosing regimen.

L15 ANSWER 7 OF 17 MEDLINE on STN DUPLICATE 3
ACCESSION NUMBER: 2002402056 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12152002
TITLE: Dose-dependent inhibition of CYP3A activity by clarithromycin during Helicobacter pylori eradication therapy assessed by changes in plasma lansoprazole levels and partial cortisol clearance to 6beta-hydroxycortisol.
AUTHOR: Ushiama Hideki; Echizen Hirotoshi; Nachi Shinobu; Ohnishi Akihiro
CORPORATE SOURCE: Department of Laboratory Medicine, Daisan Hospital, Jikei University School of Medicine, and the Department of Pharmacotherapy, Meiji Pharmaceutical University, Japan.
SOURCE: Clinical pharmacology and therapeutics, (2002 Jul) 72 (1) 33-43.
Journal code: 0372741. ISSN: 0009-9236.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals

ENTRY MONTH: 200208
ENTRY DATE: Entered STN: 20020802
Last Updated on STN: 20021212
Entered Medline: 20020820

AB OBJECTIVE: A 7-day triple therapy with lansoprazole, amoxicillin (INN, amoxicilline), and clarithromycin is widely used for eradication of Helicobacter pylori. Because clarithromycin is a potent inhibitor of cytochrome P450 (CYP) 3A, we investigated whether the standard triple therapy with clarithromycin would elicit clinically relevant CYP3A inhibition and alter CYP3A-mediated lansoprazole disposition in H pylori-positive patients. METHODS: Twenty H pylori-positive patients with peptic **ulcer** disease were randomly assigned to 2 groups: One group received 200 mg clarithromycin, 30 mg lansoprazole, and 750 mg amoxicillin at 8 am and 8 pm for 7 days; the other group received 400 mg clarithromycin, 30 mg lansoprazole, and 750 mg amoxicillin at 8 am and 8 pm for 7 days. Ten healthy control subjects received 30 mg lansoprazole and 750 mg amoxicillin at 8 am and 8 pm for 7 days but did not receive clarithromycin. Urine samples were collected for 3 hours (from 8 am to 11 am) for urinary 6beta-hydroxycortisol and cortisol assay, and midpoint (at 9:30 am) plasma samples for cortisol assay were obtained from all participants before the drug therapy (day 0) and on day 7. In vivo CYP3A activity was assessed by the partial cortisol clearance by means of the formation of 6beta-hydroxycortisol (CL(cortisol-->6beta-hydroxycortisol)) and the urinary 6beta-hydroxycortisol/cortisol ratio. Additional plasma samples for lansoprazole, 5-**hydroxylansoprazole**, and lansoprazole sulfone assay were obtained at 11 am on day 7. RESULTS: The groups of patients given 400 and 800 mg/day clarithromycin for H pylori eradication therapy showed 39% (from 2.20 +/- 1.29 to 1.35 +/- 0.88 mL/min [day 0 versus 7, mean +/- SD]; P <.05) and 68% (2.40 +/- 1.22 to 0.76 +/- 0.51 mL/min; P <.05) reductions in CL(cortisol-->6beta-hydroxycortisol), respectively. In contrast, the control subjects given lansoprazole and amoxicillin without clarithromycin showed no significant changes in CL(cortisol-->6beta-hydroxycortisol). The urinary 6beta-hydroxycortisol/cortisol ratio also decreased significantly (P <.05) in the patient groups but not in the control subjects. The mean 3-hour plasma lansoprazole levels elevated in proportion to the doses of clarithromycin: 385 +/- 338 ng/mL for the control subjects, 696 +/- 797 ng/mL for the H pylori-positive patients given 400 mg/day clarithromycin, and 947 +/- 806 ng/mL for the H pylori-positive patients given 800 mg/day clarithromycin (P <.05 versus the control subjects). No significant differences were observed among the groups in the mean plasma ratios of 5-**hydroxylansoprazole** or lansoprazole sulfone to lansoprazole. CONCLUSIONS: The 7-day H pylori eradication therapy with clarithromycin, amoxicillin, and lansoprazole may elicit substantial inhibition of in vivo CYP3A activity. Although resultant elevations in plasma lansoprazole concentrations may be beneficial for H pylori eradication, caution must be exercised for possible drug interaction with a concomitantly administered CYP3A substrate (s) in patients undergoing H pylori eradication therapy with clarithromycin, amoxicillin, and lansoprazole.

L15 ANSWER 8 OF 17 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 2002:139897 BIOSIS
DOCUMENT NUMBER: PREV200200139897
TITLE: Role of CYP3A4 and CYP2C19 in the stereoselective metabolism of lansoprazole by human liver microsomes.
AUTHOR(S): Katsuki, H.; Hamada, A.; Nakamura, C.; Arimori, K.; Nakano, M. [Reprint author]
CORPORATE SOURCE: Department of Pharmacy, Kumamoto University Hospital, 1-1-1 Honjo, Kumamoto, 860-8556, Japan

nakano@kaiju.medic.kumamoto-u.ac.jp
SOURCE: European Journal of Clinical Pharmacology, (December, 2001) Vol. 57, No. 10, pp. 709-715. print.
CODEN: EJCPAS. ISSN: 0031-6970.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 6 Feb 2002
Last Updated on STN: 21 Mar 2002

AB Objective: The aim of this investigation was to clarify the stereoselective properties in lansoprazole metabolism by monitoring the metabolic consumption for each enantiomer and the formation of the main metabolites, lansoprazole sulfone and 5-**hydroxylansoprazole**, in the presence of human liver microsomal enzymes. Methods: Human liver microsomes or recombinant cytochrome P450 (CYP) enzymes were incubated with either (+-)-, (+)-, or (-)-lansoprazole in the presence of reduced nicotinamide adenine dinucleotide phosphate. The metabolic consumption of lansoprazole enantiomers was estimated from the amounts of enantiomers consumed by microsomal enzymes after incubation at 37degreeC for 60 min. Metabolites of lansoprazole, lansoprazole sulfone, and 5-**hydroxylansoprazole** were determined after incubation at 37degreeC for 20 min, and kinetic parameters (Michaelis constant (Km) and maximum velocity (Vmax)) were obtained using Eadie-Hofstee plots. Results: (-)-Lansoprazole was metabolized more preferentially than (+)-lansoprazole in human liver microsomes. Stereoselective sulfoxidation ((-)>(+)) and hydroxylation ((+)>(-)) were observed in human liver microsomes. Strikingly, in sulfoxidation, a significantly higher intrinsic clearance (Vmax,1/Km,1) of (-)-lansoprazole (0.023 +- 0.001 ml/min/mg) than (+)-lansoprazole (0.006 +- 0.000 ml/min/mg) was observed. Consequently, sulfoxidation is likely to play an important role in the stereoselective metabolism of lansoprazole enantiomers. P450-isoform specificity for each enantiomer was evident. CYP3A4, which mainly catalyzed sulfoxidation, was more active toward (-)-lansoprazole in either a chiral or racemic drug as a substrate, CYP2C19, which catalyzed hydroxylation, preferentially metabolized (+)-lansoprazole. The consumption of (+)-lansoprazole was markedly inhibited by (-)-lansoprazole, indicating a metabolic enantiomer/enantiomer interaction. However, this alteration of recombinant CYP2C19 specificity for (+)-lansoprazole did not appear in metabolism in human liver microsomes. Conclusions: Stereoselective metabolism was observed in human liver microsomes, and this stereoselectivity was mainly based on CYP3A4 specificity for preferable metabolism of (-)-lansoprazole.

L15 ANSWER 9 OF 17 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED.
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ACCESSION NUMBER: 2001353862 EMBASE
TITLE: Comparison of the kinetic disposition of and serum **gastrin** change by lansoprazole versus rabeprazole during an 8-day dosing scheme in relation to CYP2C19 polymorphism.
AUTHOR: Ieiri I.; Kishimoto Y.; Okochi H.; Momiyama K.; Morita T.; Kitano M.; Morisawa T.; Fukushima Y.; Nakagawa K.; Hasegawa J.; Otsubo K.; Ishizaki T.
CORPORATE SOURCE: I. Ieiri, Department of Hospital Pharmacy, Faculty of Medicine, Tottori University, Nishi-machi 36-1, Yonago 683-8504, Japan. ieiri-ttr@umin.ac.jp
SOURCE: European Journal of Clinical Pharmacology, (2001) Vol. 57, No. 5-6, pp. 485-492.
Refs: 43
ISSN: 0031-6970 CODEN: EJCPAS

COUNTRY: Germany
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20011018
Last Updated on STN: 20011018

AB Background: Little is known about differences in the disposition kinetics and pharmacological effects on **gastrin** levels between lansoprazole and rabeprazole given in a repeated dosing scheme with respect to the polymorphic CYP2C19. Aim: To provide preliminary information that should be considered when prescribing proton-pump inhibitors (PPIs) for the treatment of acid-related diseases with reference to the CYP2C19 genotypic status. Methods: Helicobacter pylori-negative healthy volunteers were divided into the following three groups (n=5 each) on the basis of genotyping for CYP2C19: homozygous (hmEMs) and heterozygous extensive metabolizers (htEMs), and poor metabolizers (PMs). All received once-daily 30-mg doses of lansoprazole or 10-mg doses of rabeprazole during an 8-day course in a crossover manner. Results: The relative values for the area under the serum concentration-time curve (AUC) of lansoprazole and rabeprazole in the hmEMs, htEMs, and PMs after the final doses were 1:1.7:3.9 and 1:1.7:3.8, respectively. The relative AUCs of **gastrin** in the hmEMs, htEMs, and PMs were 1.6:2.6:3.1 for lansoprazole and 1.6:2.6:2.9 for rabeprazole, respectively. Conclusion: The disposition kinetic behavior of the two PPIs is co-segregated with CYP2C19. The magnitude of CYP2C19-dependent drug availability in the systemic circulation and resulting **gastrin** response appears to be fairly similar between the two drugs within the same CYP2C19 genotypic groups after a multiple-dosing regimen.

L15 ANSWER 10 OF 17 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN DUPLICATE 4

ACCESSION NUMBER: 2001:308860 BIOSIS
DOCUMENT NUMBER: PREV200100308860
TITLE: Pharmacokinetic differences between lansoprazole enantiomers and contribution of cytochrome P450 isoforms to enantioselective metabolism of lansoprazole in dogs.
AUTHOR(S): Masa, Kengo; Hamada, Akinobu; Arimori, Kazuhiko; Fujii, Junko; Nakano, Masahiro [Reprint author]
CORPORATE SOURCE: Department of Pharmacy, Kumamoto University Hospital, 1-1-1 Honjo, Kumamoto, 860-8556, Japan
nakano@kaiju.medic.kumamoto-u.ac.jp
SOURCE: Biological and Pharmaceutical Bulletin, (March, 2001) Vol. 24, No. 3, pp. 274-277. print.
ISSN: 0918-6158.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 27 Jun 2001
Last Updated on STN: 19 Feb 2002

AB The purpose of this study was to evaluate the pharmacokinetics of lansoprazole enantiomers and contribution of cytochrome P450 enzymes to enantioselective metabolism in dogs. The mean Cmax and area under the curve (AUC) values of (+)-lansoprazole were 4-5 times greater than those of (-)-lansoprazole following oral administration of 30-mg racemic lansoprazole to dogs. The CLtot/F values of (+)-lansoprazole were significantly smaller than those of (-)-lansoprazole ($p<0.05$). The mean unbound fraction of (-)-lansoprazole was significantly greater than that

of the (+)-lansoprazole. The amount of (+)-lansoprazole remaining was significantly greater than that of the (-)-lansoprazole after incubation of racemic lansoprazole in dog liver microsomes. When the effects of ticlopidine or ketoconazole on the metabolism of lansoprazole were studied using dog liver microsomes, ticlopidine significantly inhibited the formation of 5-**hydroxylansoprazole**, but not another metabolite, lansoprazole sulfone; however ketoconazole significantly inhibited formation of both metabolites. When the amount of (+)- and (-)-enantiomers remaining was measured in the presence and absence of ticlopidine, the amount of (+)-lansoprazole was significantly greater than that of the (-)-lansoprazole. On the other hand, there was no significant difference between the amount of (+)- and (-)-enantiomers remaining in combination with ketoconazole. These results suggest that the enantioselective pharmacokinetics of lansoprazole enantiomers are probably ascribable to their enantioselective protein binding and/or metabolism, and among the cytochrome P450 enzymes, CYP3A contributed to the enantioselective metabolism of lansoprazole.

L15 ANSWER 11 OF 17 MEDLINE on STN DUPLICATE 5
ACCESSION NUMBER: 1999301708 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10375172
TITLE: Effect of clarithromycin and other macrolides on the sulfoxidation and 5-hydroxylation of lansoprazole in dogs.
AUTHOR: Masa K; Arimori K; Nakayama T; Miyamoto S; Fujii J; Nakano M
CORPORATE SOURCE: Department of Pharmacy, Kumamoto University Hospital, Japan.
SOURCE: Biological & pharmaceutical bulletin, (1999 May) 22 (5) 504-9.
Journal code: 9311984. ISSN: 0918-6158.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199908
ENTRY DATE: Entered STN: 19990820
Last Updated on STN: 19990820
Entered Medline: 19990809

AB The purpose of this study was to evaluate a possible interaction between lansoprazole and clarithromycin as well as other macrolides in dogs. Lansoprazole (30 mg) was orally administered to male beagle dogs, with or without oral pretreatment with 200-mg clarithromycin twice a day for 5 d. The experiments had a randomized cross-over design with a two-week washout period between dosing regimens. Clarithromycin pretreatment for 5 d resulted in a significant increase in the area under the serum lansoprazole concentration-time curve (AUC), whereas the area for a lansoprazole metabolite, lansoprazole sulfone, was significantly reduced, as was the maximum serum concentration (Cmax) of lansoprazole sulfone. When the effects of clarithromycin on the metabolism of lansoprazole were studied using dog liver microsomes, it was found that clarithromycin significantly inhibited the formation of lansoprazole sulfone but not another metabolite, 5-**hydroxylansoprazole.** These results suggest that co-medication of lansoprazole with clarithromycin may produce a synergistic effect caused by the increased serum levels of lansoprazole of benefit in Helicobacter pylori eradication.

L15 ANSWER 12 OF 17 MEDLINE on STN DUPLICATE 6
ACCESSION NUMBER: 1999093136 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9877309

TITLE: Pharmacokinetic differences between lansoprazole enantiomers in rats.
AUTHOR: Arimori K; Yasuda K; Katsuki H; Nakano M
CORPORATE SOURCE: Department of Pharmacy, Kumamoto University Hospital, Japan.
SOURCE: Journal of pharmacy and pharmacology, (1998 Nov) 50 (11) 1241-5.
Journal code: 0376363. ISSN: 0022-3573.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199904
ENTRY DATE: Entered STN: 19990511
Last Updated on STN: 19990511
Entered Medline: 19990426

AB Because limited information is available about potential differences between the pharmacokinetics and pharmacodynamics of the enantiomers of lansoprazole, the enantioselective pharmacokinetics of the compound have been investigated in rats. There was a noticeable difference between the serum levels of the enantiomers of lansoprazole and of their metabolites, 5-**hydroxylansoprazole** enantiomers, after oral administration of the racemate (50 mg kg(-1)) to rats. Cmax (maximum serum concentration) and AUC (area under the serum concentration-time curve) for (+)-lansoprazole were 5-6 times greater than those for (-)-lansoprazole, whereas for (+)-5-**hydroxylansoprazole** both values were significantly smaller than those for the (-) enantiomer. CLtot/F values (where CLtot is total clearance and F is the fraction of the dose absorbed) for (+)-lansoprazole were significantly smaller than those for the (-) enantiomer. There was no significant difference between the absorption rate constants of the lansoprazole enantiomers in the in-situ absorption study. The in-vitro protein-binding study showed that binding of (+)-lansoprazole to rat serum proteins was significantly greater than for the (-) enantiomer. The in-vitro metabolic study showed that the mean metabolic ratio (45.9%) for (-)-lansoprazole was significantly greater than that (19.8%) for the (+) enantiomer in rat liver microsomes at 5.6 microM lansoprazole. These results show that the enantioselective disposition of lansoprazole could be a consequence of the enantioselectivity of plasma-protein binding and the hepatic metabolism of the enantiomers.

L15 ANSWER 13 OF 17 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 1997:438913 BIOSIS
DOCUMENT NUMBER: PREV199799738116
TITLE: Genetic polymorphism of CYP2C19 and lansoprazole pharmacokinetics in Japanese subjects.
AUTHOR(S): Katsuki, H.; Nakamura, C.; Arimori, K.; Fujiyama, S.; Nakano, M. [Reprint author]
CORPORATE SOURCE: Dep. Pharm., Kumamoto Univ. Hosp., 1-1-1 Honjo, Kumamoto 860, Japan
SOURCE: European Journal of Clinical Pharmacology, (1997) Vol. 52, No. 5, pp. 391-396.
CODEN: EJCPAS. ISSN: 0031-6970.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 8 Oct 1997
Last Updated on STN: 8 Oct 1997

AB Objective: We investigated whether interindividual differences in the

pharmacokinetic disposition of lansoprazole are attributed to the genetic polymorphism of CYP2C19 which occurred by two mutations, CYP2C19m1 and CYP2C19m2, in 20 Japanese subjects. Methods: Polymerase chain reaction (PCR) restriction fragment length polymorphism procedures were used to detect the CYP2C19m1 mutation in exon 5 and the CYP2C19m2 mutation in exon 4 using SmaI and BamHI, respectively. Results: Ten subjects were homozygous (wt/wt subjects) for the wt allele in both exon 5 and exon 4, four subjects were heterozygous (wt/m1) for the CYP2C19m1 mutation, and two subjects were heterozygous (wt/m2) for the CYP2C19m2. The remaining four subjects had both mutated alleles in CYP2CI9 genes, i.e., two were homozygous (m1/m1) for the defect in exon 5 and two were heterozygous (m1/m2) for the two defects in exons 5 and 4. The subjects in group 1 (wt/wt, wt/m1 and wt/m2) were the extensive metabolizers (EMs) for 5-hydroxylation of lansoprazole and were in the range of hydroxylation indexes from 3.83 to 19.8, whereas the subjects in group 2 (m1/m1 and m1/m2) were the poor metabolizers (PMs) and the indexes were in the range of 38.5 to 47.6. In group 2, AUC, t-1/2 and CL/f of lansoprazole were significantly greater, longer, and lower, respectively, than those in group 1. Conclusion: The hydroxylation of lansoprazole to 5-**hydroxylansoprazole** was apparently impaired in the subjects with the genetic defects of CYP2C19 (m1/m1 or m1/m2).

L15 . ANSWER 14 OF 17 JICST-EPlus COPYRIGHT 2005 JST on STN
ACCESSION NUMBER: 961013832 JICST-EPlus
TITLE: A Study of Inter-subject Variation of Pharmacokinetic Parameters after Lansoprazole (AG-1749) Injection. A Comparison with Diazepam i.v. Administration.
AUTHOR: NAKAMURA KOICHI; NAKANO SHIGEYUKI
NAKAMURA TSUYOSHI; MIZOROGI YOSHIHIRO; SHIRAI HIROAKI
CORPORATE SOURCE: Oita Med. Univ. Sch. of Med.
Tokokai Toda Cent. Hosp.
SOURCE: Rinsho Iyaku (Journal of Clinical Therapeutics & Medicines), (1996) vol. 12, no. 13, pp. 2775-2788. Journal Code: Y0906A (Fig. 10, Tbl. 5, Ref. 11)
ISSN: 0910-8211
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article
LANGUAGE: Japanese
STATUS: New
AB To clarify the cause of interindividual variabilities in serum concentration and elimination half-life (t1/2) observed after intravenous administration of lansoprazole (AG-1749), we compared the area under the concentration-time curve (AUC) and t1/2 of lansoprazole after i.v. administration with those of diazepam, which shows polymorphic hydroxylation by cytochrome P450 2C19, after p.o. administration. Prior to the study, 44 Japanese healthy male volunteers were given a single dose of lansoprazole (30mg) p.o. and were classified into 2 groups according to the serum concentrations of lansoprazole and its major metabolites, **hydroxylansoprazole** (M-VI) and lansoprazole sulfone (M-VII). One of the groups comprised the subjects who exhibited slower metabolism of lansoprazole (slow metabolizer, SM) with higher serum concentrations and longer t1/2 values and the other comprised the subjects whose serum lansoprazole concentrations decreased rapidly (rapid metabolizer, RM). Eight subjects from each group were then selected for participation in the study. We administered a single dose of lansoprazole (30mg) i.v. to the subjects in both groups at first. Then, after the washout period of 1 week or more, we administered a single dose of diazepam (5mg) i.v. to the same subjects. The mean AUC and t1/2 for lansoprazole and its metabolites (M-VI and M-VII) in the SM subjects differed significantly from those in the RM

subjects (p<0.001). The plasma concentration of diazepam decreased slowly in the SM subjects and rapidly in the RM subjects. The mean AUC and t1/2 for diazepam and its metabolites in the SM subjects differed significantly from those in the RM subjects (p<0.003). Scattered plots using the AUC for lansoprazole and diazepam clearly separated the subjects into the 2 groups, SM and RM. The same was true for t1/2. (author abst.)

L15 ANSWER 15 OF 17 JICST-EPlus COPYRIGHT 2005 JST on STN
ACCESSION NUMBER: 961013831 JICST-EPlus
TITLE: A Study of Inter-subject Variation of Pharmacokinetic Parameters after Lansoprazole (AG-1749) Injection. A Comparison of Lansoprazole Intravenous Administration with Omeprazole Oral Administration.
AUTHOR: NAKAMURA KOICHI; NAKANO SHIGEYUKI
NAKAMURA TSUYOSHI; MIZOROGI YOSHIHIRO
CORPORATE SOURCE: Oita Med. Univ. Sch. of Med.
Tokokai Toda Cent. Hosp.
SOURCE: Rinsho Iyaku (Journal of Clinical Therapeutics & Medicines), (1996) vol. 12, no. 13, pp. 2763-2774. Journal Code: Y0906A (Fig. 6, Tbl. 5, Ref. 17)
ISSN: 0910-8211
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article
LANGUAGE: Japanese
STATUS: New
AB To clarify the cause of interindividual variabilities in serum concentration and elimination half-life (t1/2) observed after intravenous administration of lansoprazole (AG-1749), we compared the area under the concentration-time curve (AUC) and t1/2 of lansoprazole after i.v. administration with those of omeprazole, which shows polymorphic hydroxylation by cytochrome P450 2C19, after p.o. administration. Prior to the study, 41 Japanese healthy male volunteers were given a single dose of lansoprazole (30mg) p.o. and were classified into two groups according serum concentrations of lansoprazole and its major metabolites, **hydroxylansoprazole** (M-VI) and lansoprazole sulfone (M-VII). One of the groups comprised the subjects who exhibited slower metabolism of lansoprazole (slow metabolizer, SM), with higher serum concentrations and longer t1/2 values and the other comprised the subjects whose serum lansoprazole concentrations decreased rapidly (rapid metabolizer, RM). Eight subjects from each group were then selected for participation in the study. We administered a single dose of lansoprazole (30mg) i.v. or omeprazole (20mg) p.o. to the subjects in both groups in a cross-over design. The mean AUC and t1/2 for lansoprazole and its metabolites (M-VI and M-VII) in the SM subjects differed significantly from those in the RM subjects (p<0.01). The plasma concentrations of omeprazole decreased slowly in the SM subjects and rapidly in the RM subjects. The mean AUC and t1/2 for omeprazole and its metabolites in the SM subjects differed significantly from those in the RM subjects (p<0.01). Scattered plots using the AUC for lansoprazole and omeprazole clearly separated the subjects into the two groups, SM and RM. The same was true for t1/2. (author abst.)

L15 ANSWER 16 OF 17 JICST-EPlus COPYRIGHT 2005 JST on STN
ACCESSION NUMBER: 961013830 JICST-EPlus
TITLE: Clinical Pharmacological Study of Lansoprazole Injection. Concerning the Pharmacokinetics in the Elderly.
AUTHOR: NAKAMURA TSUYOSHI; SHIRAI HIROAKI
NAKAMURA KOICHI
CORPORATE SOURCE: Tokokai Toda Cent. Hosp.

Oita Med. Univ. Sch. of Med.
SOURCE: Rinsho Iyaku (Journal of Clinical Therapeutics & Medicines), (1996) vol. 12, no. 13, pp. 2755-2762. Journal Code: Y0906A (Fig. 3, Tbl. 5, Ref. 5)
ISSN: 0910-8211
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article
LANGUAGE: Japanese
STATUS: New

AB In 10 healthy male volunteers aged 65 years and elder, a single dose of 15mg of lansoprazole injection was intravenously given to investigate the pharmacokinetics and safety. As in the case of non-elderly healthy male volunteers, lansoprazole was mainly present in serum. The metabolites, M-VI (**hydroxylansoprazole**) and M-VII (lansoprazole sulfone), were detected in small quantities. The serum concentrations of the intact from of lansoprazole decreased biphasically. The elimination half-life (t1/2B) was 2.28 hours. Lansoprazole was almost completely disappeared from the serum at 24 hours postdose. The area under the serum concentration-time curve (AUC0-24) was also about the same as that in non-elderly healthy male volunteers. Lansoprazole was not detected in urine, while the metabolites M-IV, M-VI and M-IX were detected. The cumulative urinary excretion at 24 hours postdose was about 9% of dose, which was a little less than that in non-elderly healthy male volunteers. The safety evaluation revealed slight elevations of GPT and Γ-GTP in one subject at follow up of a week after the administration. Since their relationships with the study drug were not completely denied, the causal relation was assessed as "possible". They were, however, mild in severity and considered to have no problem as there was no abnormal alteration after the study treatment. No adverse reactions of signs and symptoms were observed at all. The above results indicate that there is no much difference between the elderly healthy male volunteers and the non-elderly healthy male volunteers. Hence, the clinical application of lansoprazole for the elderly patients was considered possible in the same dosage regimen as that for the non-elderly. (author abst.)

L15 ANSWER 17 OF 17 MEDLINE on STN DUPLICATE 7
ACCESSION NUMBER: 96210080 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8627562
TITLE: Identification of the human P450 enzymes involved in lansoprazole metabolism.
AUTHOR: Pearce R E; Rodrigues A D; Goldstein J A; Parkinson A
CORPORATE SOURCE: Department of Pharmacology, Toxicology and Therapeutics, University of Kansas Medical Center, Kansas City, USA.
CONTRACT NUMBER: ES03765 (NIEHS)
ES07079 (NIEHS)
GM37044 (NIGMS)
SOURCE: Journal of pharmacology and experimental therapeutics, (1996 May) 277 (2) 805-16.
Journal code: 0376362. ISSN: 0022-3565.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199606
ENTRY DATE: Entered STN: 19960708
Last Updated on STN: 19960708
Entered Medline: 19960627

AB The aim of this study was to identify which human P450 enzymes are involved in the metabolism of lansoprazole. In the presence of NADPH and

oxygen, human liver microsomes converted lansoprazole to lansoprazole sulfide, lansoprazole sulfone and 5-**hydroxylansoprazole.**
Formation of lansoprazole sulfide occurred nonenzymatically. The formation of lansoprazole sulfone appeared to be catalyzed by a single, low-affinity enzyme (apparent Km approximately 100 microM). In contrast, lansoprazole 5-hydroxylation appeared to be catalyzed by two kinetically distinct enzymes (apparent Km approximately 100 microM and approximately 15 microM). When human liver microsomes (n = 16) were incubated with 100 microM lansoprazole, both the 5-hydroxylation and sulfoxidation of lansoprazole appeared to be catalyzed by CYP3A4/5 (based on correlation analyses). Antibodies against rat CYP3A enzymes inhibited the rate of both 5-hydroxylation (approximately 55%) and sulfoxidation (approximately 70%) and cDNA-expressed CYP3A4 catalyzed both the 5-hydroxylation and sulfoxidation of lansoprazole (apparent Km approximately 100 microM). However, at the pharmacologically relevant substrate concentration of 1 microM, lansoprazole sulfoxidation was still highly correlated with CYP3A4/5 activity (r2 = .905), but lansoprazole 5-hydroxylation appeared to be catalyzed by CYP2C19 (r2 = .875) rather than CYP3A4/5 (r2 = .113). Antibodies and chemical inhibitors of CYP2C enzymes preferentially inhibited the 5-hydroxylation of lansoprazole, whereas lansoprazole sulfoxidation was preferentially inhibited by antibodies and chemical inhibitors of CYP3A4/5. The cDNA expressed enzymes CYP2C8, CYP2C9 and CYP2C19 catalyzed varying rates of lansoprazole 5-hydroxylation at a substrate concentration of 50 microM, but only CYPC19 catalyzed this reaction at 1 microM. These results suggest that at pharmacologically relevant concentrations, the 5-hydroxylation of lansoprazole is primarily catalyzed by CYP2C19, whereas the sulfoxidation of lansoprazole is primarily catalyzed by CYP3A4/5. It is possible that individuals lacking CYP2C19 will be poor metabolizers of lansoprazole.

```
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L10             1 SEA FILE=REGISTRY ABB=ON  131926-98-2/RN
L11            33 SEA FILE=HCAPLUS ABB=ON  L10 OR ?HYDROXYLANSOPRAZOLE?
L12            10 SEA FILE=HCAPLUS ABB=ON  L11 AND (?ULCER? OR ?GASTR? OR
                  ?ESOPHAG?)
L16             3 SEA FILE=USPATFULL ABB=ON  L12 AND (PRD<20031014 OR PD<20031014
                  )
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L16  ANSWER 1 OF 3  USPATFULL on STN
ACCESSION NUMBER:         2004:101818  USPATFULL
TITLE:                    Hydroxylansoprazole methods
INVENTOR(S):              Yelle, William E., Billerica, MA, UNITED STATES
PATENT ASSIGNEE(S):       SEPRACOR INC., Marlborough, MA (U.S. corporation)

                               NUMBER         KIND    DATE
                          ---------------- ------ --------
PATENT INFORMATION:       US 2004077688      A1   20040422
APPLICATION INFO.:        US 2003-685628     A1   20031014  (10)
RELATED APPLN. INFO.:     Continuation of Ser. No. US 2001-46464, filed on 19 Oct
                          2001, ABANDONED Division of Ser. No. US 1999-357458,
                          filed on 20 Jul 1999, GRANTED, Pat. No. US 6335351

                                 NUMBER         DATE
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PRIORITY INFORMATION:     US 1998-93762P     19980722 (60)          <--
DOCUMENT TYPE:            Utility
FILE SEGMENT:             APPLICATION
LEGAL REPRESENTATIVE:     HESLIN ROTHENBERG FARLEY & MESITI PC, 5 COLUMBIA
                          CIRCLE, ALBANY, NY, 12203
NUMBER OF CLAIMS:         15
EXEMPLARY CLAIM:          1
LINE COUNT:               405
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB      Methods and compositions are disclosed utilizing
        hydroxylansoprazole for the treatment of ulcers in
        humans. Hydroxylansoprazole exhibits a lessened liability
        toward drug-drug interactions than lansoprazole and a more predictable
        dosing regimen than lansoprazole. Hydroxylansoprazole is also
        useful for the treatment of gastroesophageal reflux and other
        conditions related to gastric hypersecretion such as
        Zollinger-Ellison Syndrome.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L16  ANSWER 2 OF 3  USPATFULL on STN
ACCESSION NUMBER:         2002:186157  USPATFULL
TITLE:                    Hydroxylansoprazole methods
INVENTOR(S):              Yelle, William E., Billerica, MA, UNITED STATES
PATENT ASSIGNEE(S):       SEPRACOR INC., Marlborough, MA, UNITED STATES (U.S.
                          corporation)

                               NUMBER         KIND    DATE
                          ---------------- ------ --------
PATENT INFORMATION:       US 2002099079      A1   20020725          <--
APPLICATION INFO.:        US 2001-46464      A1   20011019  (10)
RELATED APPLN. INFO.:     Division of Ser. No. US 1999-357458, filed on 20 Jul
                          1999, PATENTED
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	NUMBER	DATE
PRIORITY INFORMATION:	US 1998-93762P	19980722 (60) <--
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	Philip E. Hansen, Heslin Rothenberg Farley & Mesiti P.C., 5 Columbia Circle, Albany, NY, 12203	
NUMBER OF CLAIMS:	15	
EXEMPLARY CLAIM:	1	
LINE COUNT:	407	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Methods and compositions are disclosed utilizing **hydroxylansoprazole** for the treatment of **ulcers** in humans. **Hydroxylansoprazole** exhibits a lessened liability toward drug-drug interactions than lansoprazole and a more predictable dosing regimen than lansoprazole. **Hydroxylansoprazole** is also useful for the treatment of **gastroesophageal** reflux and other conditions related to **gastric** hypersecretion such as Zollinger-Ellison Syndrome.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L16 ANSWER 3 OF 3 USPATFULL on STN

ACCESSION NUMBER:	2002:1245 USPATFULL			
TITLE:	**Hydroxylansoprazole** compositions and methods			
INVENTOR(S):	Yelle, William E., Littleton, MA, United States			
PATENT ASSIGNEE(S):	Sepracor Inc., Marlborough, MA, United States (U.S. corporation)			
	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6335351	B1	20020101	<--
APPLICATION INFO.:	US 1999-357458		19990720 (9)	

	NUMBER	DATE	
PRIORITY INFORMATION:	US 1998-93762P	19980722 (60)	<--
	US 1998-93762P	19980722 (60)	<--
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	GRANTED		
PRIMARY EXAMINER:	Cook, Rebecca		
LEGAL REPRESENTATIVE:	Heslin Rothenberg Farley & Mesiti P.C.		
NUMBER OF CLAIMS:	6		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	0 Drawing Figure(s); 0 Drawing Page(s)		
LINE COUNT:	364		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Methods and compositions are disclosed utilizing **hydroxylansoprazole** for the treatment of **ulcers** in humans. **Hydroxylansoprazole** exhibits a lessened liability toward drug-drug interactions than lansoprazole and a more predictable dosing regimen than lansoprazole. **Hydroxylansoprazole** is also usefull for the treatment of **gastroesophageal** reflux and other conditions related to **gastric** hypersecretion such as Zollinger-Ellison Syndrome.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

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=> d his ful

     (FILE 'HOME' ENTERED AT 17:37:14 ON 24 AUG 2005)

     FILE 'HCAPLUS' ENTERED AT 17:37:22 ON 24 AUG 2005
                E YELLE WILLIAM E/AU
L1             18 SEA ABB=ON  "YELLE WILLIAM E"/AU
L2              1 SEA ABB=ON  L1 AND ?HYDROXYLANSOPRAZOL?
L3              6 SEA ABB=ON  L1 AND ?GASTROESOPHAG?
L4              6 SEA ABB=ON  L2 OR L3
L5                ANALYZE L4 1-6 CT :       7 TERMS

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L7              0 SEA ABB=ON  5-HYDROXYANSOPRAZOLE/CN
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L10             1 SEA ABB=ON  131926-98-2/RN

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L14            26 SEA ABB=ON  L12
L15            17 DUP REMOV L14 (9 DUPLICATES REMOVED)   17 cits from above d.b.'s

     FILE 'USPATFULL' ENTERED AT 17:54:00 ON 24 AUG 2005
L16             3 SEA ABB=ON  L12 AND (PRD<20031014 OR PD<20031014)
                              3 cits from USPatFull
     FILE HOME

     FILE HCAPLUS

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     FILE LAST UPDATED: 23 Aug 2005  (20050823/ED)

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      substance identification.
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DICTIONARY FILE UPDATES: 23 AUG 2005 HIGHEST RN 861509-89-9

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* *
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http://www.cas.org/ONLINE/DBSS/registryss.html

FILE MEDLINE
FILE LAST UPDATED: 24 AUG 2005 (20050824/UP). FILE COVERS 1950 TO DATE.

On December 19, 2004, the 2005 MeSH terms were loaded.

The MEDLINE reload for 2005 is now available. For details enter HELP RLOAD at an arrow promt (=>). See also:

http://www.nlm.nih.gov/mesh/
http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html

OLDMEDLINE now back to 1950.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2005 vocabulary.

This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE CANCERLIT
FILE COVERS 1963 TO 15 Nov 2002 (20021115/ED)

On July 28, 2002, CANCERLIT was reloaded. See HELP RLOAD for details.

CANCERLIT thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2002 vocabulary. Enter HELP THESAURUS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE BIOSIS
FILE COVERS 1969 TO DATE.
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT
FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 17 August 2005 (20050817/ED)

FILE RELOADED: 19 October 2003.

FILE EMBASE
FILE COVERS 1974 TO 18 Aug 2005 (20050818/ED)

EMBASE has been reloaded. Enter HELP RLOAD for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE JAPIO
FILE LAST UPDATED: 2 AUG 2005 <20050802/UP>
FILE COVERS APR 1973 TO APRIL 28, 2005

<<< GRAPHIC IMAGES AVAILABLE >>>

FILE JICST-EPLUS
FILE COVERS 1985 TO 22 AUG 2005 (20050822/ED)

THE JICST-EPLUS FILE HAS BEEN RELOADED TO REFLECT THE 1999 CONTROLLED TERM (/CT) THESAURUS RELOAD.

FILE USPATFULL
FILE COVERS 1971 TO PATENT PUBLICATION DATE: 23 Aug 2005 (20050823/PD)
FILE LAST UPDATED: 23 Aug 2005 (20050823/ED)
HIGHEST GRANTED PATENT NUMBER: US6934966
HIGHEST APPLICATION PUBLICATION NUMBER: US2005183181
CA INDEXING IS CURRENT THROUGH 23 Aug 2005 (20050823/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 23 Aug 2005 (20050823/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Jun 2005
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Jun 2005

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>>> /PK, etc. <<<

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>>> enter this cluster. <<<
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>>> classifications, or claims, that may potentially change from <<<
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Inventor Search

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L4 ANSWER 1 OF 6 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER:	2000:84622 HCAPLUS
DOCUMENT NUMBER:	132:141954
TITLE:	Pharmaceutical compositions comprising **hydroxylansoprazole** for ulcer treatment
INVENTOR(S):	**Yelle, William E.**
PATENT ASSIGNEE(S):	Sepracor Inc., USA
SOURCE:	PCT Int. Appl., 18 pp. CODEN: PIXXD2
DOCUMENT TYPE:	Patent
LANGUAGE:	English
FAMILY ACC. NUM. COUNT:	1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000004904	A1	20000203	WO 1999-US16322	19990719
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2337886	AA	20000203	CA 1999-2337886	19990719
AU 9952182	A1	20000214	AU 1999-52182	19990719
AU 763642	B2	20030731		
EP 1098648	A1	20010516	EP 1999-937321	19990719
EP 1098648	B1	20021002		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002521336	T2	20020716	JP 2000-560897	19990719
AT 225175	E	20021015	AT 1999-937321	19990719
ES 2182554	T3	20030301	ES 1999-937321	19990719
US 6335351	B1	20020101	US 1999-357458	19990720
US 2002099079	A1	20020725	US 2001-46464	20011019
US 2004077688	A1	20040422	US 2003-685628	20031014

PRIORITY APPLN. INFO.:		
US 1998-93762P	P	19980722
WO 1999-US16322	W	19990719
US 1999-357458	A3	19990720
US 2001-46464	B1	20011019

AB A pharmaceutical composition for treating humans suffering from ulcers of stomach, duodenum, and esophagus, **gastroesophageal** reflux diseases, Zollinger-Ellison Syndrome, and other disorders associated with gastric hyperactivity comprises 5-**hydroxylansoprazole** or a pharmaceutically acceptable salt thereof. **Hydroxylansoprazole** exhibits a lessened liability toward drug-drug interactions and a more predictable dosing regimen than its parent compound, lansoprazole. **Hydroxylansoprazole** inhibits the H+,K+-ATPase associated with the gastric proton pump and the resulting secretion of gastric acid by parietal cells. The invention also relates to a method of treating psoriasis using **hydroxylansoprazole.** A dry granulate, prepared from dry mixture containing **hydroxylansoprazole** 250 mg, colloidal silica 8 mg, and Mg stearate 1 mg, was mixed with croscarmellose 60 mg, crystalline cellulose 190 mg, and talc 10 mg and compressed into tablets.

IC ICM A61K031-44
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1
ST **hydroxylansoprazole** pharmaceutical gastric hyperactivity psoriasis; ulcer inhibitor **hydroxylansoprazole** pharmaceutical
IT Pancreas, neoplasm
(Zollinger-Ellison syndrome; compns. containing **hydroxylansoprazole** for treatment of disorders associated with gastric hyperactivity)
IT Drug delivery systems
(capsules; compns. containing **hydroxylansoprazole** for treatment of disorders associated with gastric hyperactivity)
IT Antiulcer agents
(compns. containing **hydroxylansoprazole** for treatment of disorders associated with gastric hyperactivity)
IT Psoriasis
(compns. containing **hydroxylansoprazole** for treatment of disorders associated with gastric hyperactivity and psoriasis)
IT Digestive tract
(**gastroesophageal** reflux; compns. containing **hydroxylansoprazole** for treatment of disorders associated with gastric hyperactivity)
IT Drug delivery systems
(oral, sustained release; compns. containing **hydroxylansoprazole** for treatment of disorders associated with gastric hyperactivity)
IT Gastric acid
(secretion, hypersecretion; compns. containing **hydroxylansoprazole** for treatment of disorders associated with gastric hyperactivity)
IT Drug delivery systems
(tablets, enteric-coated; compns. containing **hydroxylansoprazole** for treatment of disorders associated with gastric hyperactivity)
IT Drug delivery systems
(tablets; compns. containing **hydroxylansoprazole** for treatment of disorders associated with gastric hyperactivity)
IT 131926-98-2, 5-**Hydroxylansoprazole** 220609-28-9 220609-30-3
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compns. containing **hydroxylansoprazole** for treatment of disorders associated with gastric hyperactivity)
IT 9000-83-3
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(proton-translocating, inhibitors; compns. containing **hydroxylansoprazole** for treatment of disorders associated with gastric hyperactivity)
REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 2 OF 6 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:722899 HCAPLUS
DOCUMENT NUMBER: 131:327572
TITLE: Desmethylpantoprazole compositions and methods
INVENTOR(S): **Yelle, William E.**
PATENT ASSIGNEE(S): Sepracor Inc., USA
SOURCE: PCT Int. Appl., 25 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 9956748	A1	19991111	WO 1999-US9815		19990505
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM					
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG					
CA 2329925	AA	19991111	CA 1999-2329925		19990505
AU 9938824	A1	19991123	AU 1999-38824		19990505
AU 747167	B2	20020509			
EP 1075262	A1	20010214	EP 1999-921682		19990505
EP 1075262	B1	20050810			
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI					
JP 2002513758	T2	20020514	JP 2000-546774		19990505
PRIORITY APPLN. INFO.:			US 1998-84249P	P	19980505
			WO 1999-US9815	W	19990505

AB Methods and compns. are disclosed utilizing desmethylpantoprazole for the treatment of ulcers in humans. Desmethylpantoprazole exhibits a lessened liability toward drug-drug interactions than pantoprazole and a more predictable dosing regimen than pantoprazole. Desmethylpantoprazole is also useful for the treatment of **gastroesophageal** reflux and other conditions related to gastric hypersecretion such as Zollinger-Ellison Syndrome.

IC ICM A61K031-44
CC 63-6 (Pharmaceuticals)
ST antiulcer tablet desmethylpantoprazole
IT Pancreas, neoplasm
(Zollinger-Ellison syndrome, treatment of; desmethylpantoprazole for treatment of gastric disorders and psoriasis)
IT Drug delivery systems
(capsules; desmethylpantoprazole for treatment of gastric disorders and psoriasis)
IT Antiulcer agents
(desmethylpantoprazole for treatment of gastric disorders and psoriasis)
IT Digestive tract
(**gastroesophageal** reflux, treatment of; desmethylpantoprazole for treatment of gastric disorders and psoriasis)
IT Drug delivery systems
(parenterals; desmethylpantoprazole for treatment of gastric disorders and psoriasis)
IT Gastric acid
(secretion, hypersecretion, treatment of; desmethylpantoprazole for treatment of gastric disorders and psoriasis)
IT Drug delivery systems
(tablets; desmethylpantoprazole for treatment of gastric disorders and psoriasis)
IT Psoriasis
(treatment of; desmethylpantoprazole for treatment of gastric disorders and psoriasis)
IT 141854-24-2 249562-49-0 249562-50-3
RL: BAC (Biological activity or effector, except adverse); BSU (Biological

study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(desmethylpantoprazole for treatment of gastric disorders and psoriasis)
REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 3 OF 6 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:722897 HCAPLUS
DOCUMENT NUMBER: 131:327571
TITLE: Hydroxyomeprazole compositions for the treatment of ulcers
INVENTOR(S): **Yelle, William E.**; Handley, Dean A.
PATENT ASSIGNEE(S): Sepracor Inc., USA
SOURCE: PCT Int. Appl., 19 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9956746	A1	19991111	WO 1999-US9814	19990505
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2330049	AA	19991111	CA 1999-2330049	19990505
AU 9939716	A1	19991123	AU 1999-39716	19990505
AU 748872	B2	20020613		
EP 1082114	A1	20010314	EP 1999-922802	19990505
EP 1082114	B1	20020828		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
AT 222764	E	20020915	AT 1999-922802	19990505
ES 2182524	T3	20030301	ES 1999-922802	19990505
JP 2003517434	T2	20030527	JP 2000-546772	19990505
US 6294586	B1	20010925	US 2000-699597	20001030
US 2002010196	A1	20020124	US 2001-927954	20010810
US 6498171	B2	20021224		

PRIORITY APPLN. INFO.:
US 1998-84258P P 19980505
WO 1999-US9814 W 19990505
US 2000-699597 A3 20001030

AB Compns. hydroxyomeprazole for the treatment of ulcers in humans are disclosed. Hydroxyomeprazole has a lower tendency towards drug-drug interactions than omeprazole and a more predictable dosing regimen than omeprazole. Hydroxyomeprazole is also useful for the treatment of gastro-esophageal reflux and other conditions related to gastric hypersecretion such as Zollinger-Ellison syndrome. Thus, tablets contained/tablet hydroxyomeprazole 250, croscarmellose 60, colloidal silicon dioxide 8, magnesium stearate 1, microcryst. cellulose 190, croscarmellose 15, and talc 10 mg.
IC ICM A61K031-415

ICS A61K031-44
CC 63-6 (Pharmaceuticals)
ST hydroxyomeprazole pharmaceutical ulcer treatment; gastric hypersecretion hydroxyomeprazole pharmaceutical
IT Pancreas, neoplasm
(Zollinger-Ellison syndrome; hydroxyomeprazole compns. for treatment of ulcers)
IT Drug delivery systems
(capsules; hydroxyomeprazole compns. for treatment of ulcers)
IT Digestive tract
(**gastroesophageal** reflux; hydroxyomeprazole compns. for treatment of ulcers)
IT Antiulcer agents
Stomach, disease
(hydroxyomeprazole compns. for treatment of ulcers)
IT Drug delivery systems
(oral; hydroxyomeprazole compns. for treatment of ulcers)
IT Drug delivery systems
(parenterals; hydroxyomeprazole compns. for treatment of ulcers)
IT Gastric acid
(secretion, hypersecretion; hydroxyomeprazole compns. for treatment of ulcers)
IT Drug delivery systems
(suspensions; hydroxyomeprazole compns. for treatment of ulcers)
IT Drug delivery systems
(tablets, enteric-coated; hydroxyomeprazole compns. for treatment of ulcers)
IT Drug delivery systems
(tablets; hydroxyomeprazole compns. for treatment of ulcers)
IT 92340-57-3, Hydroxyomeprazole 196489-26-6 196489-27-7
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(hydroxyomeprazole compns. for treatment of ulcers)
REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 4 OF 6 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:708556 HCAPLUS
DOCUMENT NUMBER: 131:327495
TITLE: R-(+)-rabeprazole as antiulcer drug
INVENTOR(S): **Yelle, William E.**; Rubin, Paul D.; Koch, Patrick
PATENT ASSIGNEE(S): Sepracor Inc., USA
SOURCE: PCT Int. Appl., 20 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9955157	A1	19991104	WO 1999-US9205	19990428

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK,

ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

CA 2330139	AA	19991104	CA 1999-2330139	19990428
AU 9938705	A1	19991116	AU 1999-38705	19990428
EP 1073332	A1	20010207	EP 1999-921512	19990428
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2002512262	T2	20020423	JP 2000-545374	19990428
PRIORITY APPLN. INFO.:			US 1998-83725P	P 19980430
			WO 1999-US9205	W 19990428

AB Methods and compns. are disclosed utilizing optically pure (+)-rabeprazole for the treatment of ulcers in humans, while reducing the concomitant adverse effects associated with the racemic mixture of rabeprazole. The optically pure (+)-isomer is also useful for the treatment of **gastroesophageal** reflux. (+)-Rabeprazole is an inhibitor of H+ release and is therefore useful in the treatment of other conditions related to gastric hypersecretion such as Zollinger-Ellison Syndrome.

IC ICM A01N043-40
CC 63-5 (Pharmaceuticals)
ST rabeprazole optically pure antiulcer drug
IT Antiulcer agents
(R-(+)-rabeprazole as antiulcer drug)
IT Pancreas, neoplasm
(Zollinger-Ellison syndrome; treatment with R-(+)-rabeprazole)
IT Digestive tract
(**gastroesophageal** reflux; treatment with R-(+)-rabeprazole)
IT 177795-60-7, R-(+)-Rabeprazole
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(R-(+)-rabeprazole as antiulcer drug)
REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 5 OF 6 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:495176 HCAPLUS
DOCUMENT NUMBER: 131:134656
TITLE: R-lansoprazole compositions and methods
INVENTOR(S): Barberich, Timothy J.; **Yelle, William E.**; Rubin, Paul D.
PATENT ASSIGNEE(S): Sepracor Inc., USA
SOURCE: PCT Int. Appl., 23 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9938513	A1	19990805	WO 1999-US1938	19990129
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2320963	AA	19990805	CA 1999-2320963	19990129
AU 9923493	A1	19990816	AU 1999-23493	19990129

AU 742620	B2	20020110		
EP 1056456	A1	20001206	EP 1999-903485	19990129
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2002501897	T2	20020122	JP 2000-529246	19990129
US 2002042433	A1	20020411	US 2001-981108	20011017
US 2003008903	A1	20030109	US 2002-216962	20020812
PRIORITY APPLN. INFO.:			US 1998-73140P	P 19980130
			US 1999-240973	B1 19990129
			WO 1999-US1938	W 19990129
			US 2000-721086	A1 20001122
			US 2001-981108	B1 20011017

AB Methods and compns. are disclosed utilizing optically pure (+)-lansoprazole for the treatment of ulcers in humans while substantially reducing the concomitant liability of adverse effects associated with the racemic mixture of lansoprazole. The optically pure (+)-isomer is also useful for the treatment of **gastroesophageal** reflux. (+)-Lansoprazole is an inhibitor of H+ release and is therefore useful in the treatment of other conditions related to gastric hypersecretion such as Zollinger-Ellison Syndrome.

IC ICM A61K031-44

CC 63-6 (Pharmaceuticals)

ST oral antiulcer optically pure R lansoprazole

IT Pancreas, neoplasm
(Zollinger-Ellison syndrome; oral compns. containing optically pure R-lansoprazole)

IT Drug delivery systems
(capsules; oral compns. containing optically pure R-lansoprazole)

IT Digestive tract
(**gastroesophageal** reflux; oral compns. containing optically pure R-lansoprazole)

IT Antiulcer agents
(oral compns. containing optically pure R-lansoprazole)

IT Drug delivery systems
(oral, granules; oral compns. containing optically pure R-lansoprazole)

IT Drug delivery systems
(tablets; oral compns. containing optically pure R-lansoprazole)

IT 138530-94-6, (+)-Lansoprazole
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(oral compns. containing optically pure R-lansoprazole)

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 6 OF 6 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER:	1999:495175 HCAPLUS
DOCUMENT NUMBER:	131:134655
TITLE:	S-lansoprazole compositions and methods
INVENTOR(S):	Barberich, Timothy J.; **Yelle, William E.**; Rubin, Paul D.
PATENT ASSIGNEE(S):	Sepracor Inc., USA
SOURCE:	PCT Int. Appl., 23 pp. CODEN: PIXXD2
DOCUMENT TYPE:	Patent
LANGUAGE:	English
FAMILY ACC. NUM. COUNT:	1
PATENT INFORMATION:	

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9938512	A1	19990805	WO 1999-US1920	19990129
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2320902	AA	19990805	CA 1999-2320902	19990129
AU 9924818	A1	19990816	AU 1999-24818	19990129
EP 1056457	A1	20001206	EP 1999-904418	19990129
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2002501896	T2	20020122	JP 2000-529245	19990129
US 2001025107	A1	20010927	US 2001-854065	20010511
US 2004224989	A1	20041111	US 2004-863532	20040608
PRIORITY APPLN. INFO.:			US 1998-73141P	P 19980130
			US 1998-107460P	P 19981105
			US 1999-240262	A1 19990129
			WO 1999-US1920	W 19990129
			US 2001-854065	B1 20010511

AB Methods and compns. are disclosed utilizing optically pure (-)-lansoprazole for the treatment of ulcers in humans while substantially reducing the concomitant liability of adverse effects associated with the racemic mixture of lansoprazole. The optically pure (-) isomer is also useful for the treatment of **gastroesophageal** reflux. (-)-Lansoprazole is an inhibitor of H+ release and is therefore useful in the treatment of other conditions related to gastric hypersecretion such as Zollinger-Ellison Syndrome.

IC ICM A61K031-44

CC 63-6 (Pharmaceuticals)

ST oral antiulcer optically pure S lansoprazole

IT Pancreas, neoplasm
(Zollinger-Ellison syndrome; oral compns. containing optically pure S-lansoprazole)

IT Drug delivery systems
(capsules; oral compns. containing optically pure S-lansoprazole)

IT Digestive tract
(**gastroesophageal** reflux; oral compns. containing optically pure S-lansoprazole)

IT Antiulcer agents
(oral compns. containing optically pure S-lansoprazole)

IT Drug delivery systems
(oral, granules; oral compns. containing optically pure S-lansoprazole)

IT Drug delivery systems
(tablets; oral compns. containing optically pure S-lansoprazole)

IT 138530-95-7, (-)-Lansoprazole
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(oral compns. containing optically pure S-lansoprazole)

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT